FORM PTO–1449	ATTY. DOCKET NO.	SERIAL NO.
LIST OF PATENTS AND OTHER ITEMS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	892,280-499	Not Yet Assigned
	APPLICANT: LAZZARINI et	
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U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE
	AA	6,551,591	04/2003	Lee			

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES	TRANSLATION NO
	AB	EP 0 592 835	04/1994	Europe				
	AC	JP 59 198982	11/1984	Japan				X

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	AD	Database WPI Section Ch, Week 198451, Derwent Publications Ltd., London, GB, Class B04, AN 1984-316058
	AF	HAYAKAWA, M. et al. "Distribution of antibiotic-producing Microbispora strains in soils with different pHs" ACTINOMYCETES 6(3): 75-79 (1995)
	AG	LAZZARINI, A. et al. "Rare genera of actinomycetes as potential producers of new antibiotics" Antonie Van Leeuwenhoek 78(3-4): 399-405 (Dec 2000)
	AH	McAULIFFE, O. et al. "Lantibiotics: structure, biosynthesis and mode of action" FEMS MICROBIOLOGY REVIEWS 25(3): 285-308 (May 2001)
	AI	SAHL, H-G. et al. "Lantibiotics : Biosynthesis and Biological Activities of Uniquely Modified Peptides from Gram-Positive Bacteria" ANN. REV. MICROBIOL. 52:41-79 (1998)
	AJ	XU, S-Z et al. "Isolation of the genus Microbispora from soil of China" WEISHENGU XUEBAO 19(3): 255-58 (1979)

EXAMINER:	DATE CONSIDERED:

EXAMINER: Initial if reference is considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include a copy of this form with next communication to applicant.

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The microorganism(s) has (have) been deposited with American Type Culture Collection under number(s) ATCC 55327.

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(54) BU-4803T Antibiotics.

(57) The present invention relates to antitumor antibiotics designated as BU-4803T A_1, A_2, B, C_1, C_2 and D. BU-4803T A_1, A_2 and B are produced by fermentation of Microbispora strain AA9968 which has been deposited with the American Type Culture Collection under the accession number ATCC 55327.

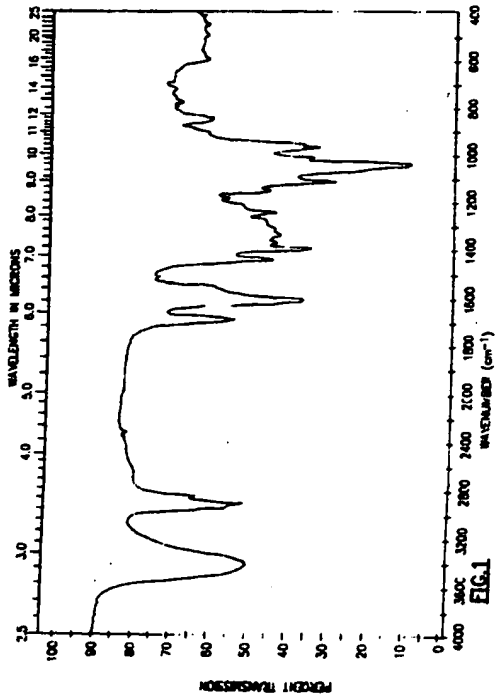

FIG.1

EP 0 592 835 A2

⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭59—198982

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C 12 R 1/01)		

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審査請求　未請求

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⑭新抗生物質ＳＦ－2240物質およびその製造法

⑳特　　願　昭58－73886

㉒出　　願　昭58(1983)4月28日

㉓発 明 者　大場和則
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東京都中央区京橋2丁目4番16号

㉚代 理 人　弁理士　久保田藤郎

明　細　書

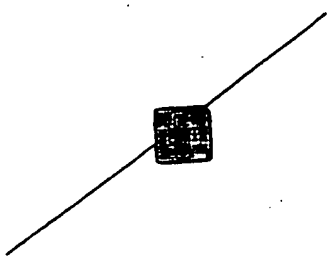
1. 発明の名称

新抗生物質SP-2240物質およびその製造法

2. 特許請求の範囲

1) 下記の特性を有する新抗生物質SP-2240物質およびその酸付加塩。

元素組成として重量比で炭素53.13%，水素6.15%，窒素16.26%，酸素24.75%を含み，質量分析（FD-MS）から分子量は591で，分子式は$C_{26}H_{37}N_7O_8$であり，水溶液中での紫外部吸収スペクトルは第1図に示すように243 nm，240 nm，260 nm（肩），303 nmに極大吸収を有し，第2図に示すような赤外部吸収スペクトルを示し，外観は白色粉末であり，水，メタノール，エタノールに可溶で，ベンゼン，酢酸エチル，ヘキサン等の有機溶媒に難溶であり，シリカゲル薄層クロマトグラムのRf値は展開溶媒n-プロパノール-ピリジン-酢酸-水（15：10：3：12）で0.75であり，n-ブタノール-メタノール-水（4：1：2）で0.19を示し，レミュー，硫酸，ニンヒドリン，ダライター-リーパッタ試薬は陽性，坂口反応は陰性であり，水溶液中での比旋光度が$[\alpha]_D^{25}$ ＋16.3°（C 1，H_2O）であり，pH 6.4ピリジン-酢酸緩衝液を用いた高電圧戸紙電気泳動（3000 V，15分間）は陰極側に5.2 cm泳動し，そのRm（リジン）は0.53で，塩基性の物質であり，第3図で実質的に代表される水素核磁気共鳴吸収スペクトルを有し，第4図で実質的に代表される炭素核磁気共鳴吸収スペクトルを有し，安定性は中性からアルカリ性にかけて比較的安定であるが，酸性で不安定な水溶性塩基性である。



(C) WPI / DERWENT
AN - 1984-316058 [51]
AP - JP19830073886 19830428
CPY - MEIJ
DC - B04 D16
FS - CPI
IC - A61K35/74 ; C07G11/00 ; C12P1/06
MC - B02-Z D05-C02
M1 - [01] M421 M710 M903 M132 P220 V001
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PN - JP59198982 A 19841110 DW198451 010pp
PR - JP19830073886 19830428
RA - C1984-134892
RIC - A61K-035/74 ; C07G-011/00 ; C12P-001/06
AB - J59198982 Antibiotic SF-2240 having following physicochemical properties is new. (1) Appearance: white amorphous powder. (2) M.pt. 104-108 deg.C. (3) Elemental analysis: c 53.13%, H 6.15%, N 16.26%, O 24.75%. (4) UV spectrum, (in water): lambda-max 243 nm (E1%,1cm-199), 249 (202), 260 (shoulder), 303 (76). (5) given IR spectrum. (6) Mol. Wt. 591. (7) Mol. formula C26H37N7O9. (8) given 1H-NMR spectrum. (9) given 13C-NMR. (10) alphaD20 = +16.3 deg. (c 1, water). (11) Solubility: soluble in water, lower alcohols; sparingly soluble in EtOAc, benzene, hexane. (12) Colour reaction: positive to Lemieux reaction, H2SO4, ninhydrin; negative to Sakaguchi reagent. (13) TLC on silica gel (Merck: F254): Rf 0.75 (n-PrOH/pyridine/AcOH/water = 15:10:12), 0.19 (n-BuOH/MeOH/water = 4:1:2), 0.29 (n-BuOH/AcOH/water = 2:1:1); on cellulose (Merck: F254): Rf 0.55 (n-BuOH/MeOH/water = 4:1:2), 0.65 (i-PrOH/BuOH/water = 7:7:6). (14) High voltage paper electrophoresis: Rm (lysine) = 0.53 (pyridine/AcOH buffer, pH 6.4, 3000V, 15 mins.). (15) Amino acid analysis by acid hydrolysis (6N-HCl at 110 deg.C for 18 hrs.): serine and glycine were recognised. (16) Stability: unstable in acidic media but relatively stable in neutral or alkaline media.
- USE/ADVANTAGE - SF-2240 has weak antimicrobial actions against gram positive and negative bacteria. Acute toxicity in mice: all of 4 mice tested were alive at 200 mg/kg (i.v.).(0/0)
IW - ANTIBIOTIC PREPARATION MICROBISPORA STRAIN WEAK ANTIMICROBIAL ACTIVE GRAM POSITIVE NEGATIVE BACTERIA
IKW - ANTIBIOTIC PREPARATION MICROBISPORA STRAIN WEAK ANTIMICROBIAL ACTIVE GRAM POSITIVE NEGATIVE BACTERIA
NC - 001
OPD - 1983-04-28
ORD - 1984-11-10
PAW - (MEIJ) MEIJI SEIKA KAISHA
TI - Antibiotic SF-2240 prepd. from Microbispora strain - having weak antimicrobial activity against Gram positive and negative bacteria

Actinomycetes, 1995

DISTRIBUTION OF ANTIBIOTIC-PRODUCING *MICROBISPORA* STRAINS IN SOILS WITH DIFFERENT pHs

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ABSTRACT. A total of 439 cultures of *Microbispora* spp., freshly isolated from 117 different soil samples, were investigated for their antimicrobial activity using a humic acid-containing medium. Eighty-seven (20%) isolates were active against *Staphylococcus aureus* and only 12 (3%) against *Aspergillus niger*. The incidence of antibiotic producers increased with soil pH.

Species of the genus *Microbispora* produce longitudinal pairs of spores on the aerial mycelium (Nonomura and Ohara, 1957). Although microbisporae represent only a minor component of the actinomycete population in soil (Hayakawa *et al.*, 1988), it has been suggested that they may play a significant role in the breakdown of the recalcitrant organic polymers, such as cellulose and xylan (Waldron *et al.*, 1986; Ball and Mc Carthy, 1988). Microbisporae have also been recognised as a source of antibiotics and other bioactive compounds, such as phenazines (Gerber and Lechevalier, 1964; Tanabe *et al.* 1995), the antifungal antibiotic Sch 31828 (Patel *et al.*, 1988), cochinmicins (Lam *et al.*, 1992), and angelmicins (Uehara *et al.*, 1993).

In the search for new antibiotics, the probability of isolating novel producers is enhanced by screening substrates harbouring a rich flora of antagonistically active organisms (Kutzner, 1989). A number of researchers have pointed out a possible correlation between occurrence of antagonistic actinomycetes and nature of the isolation soil. Rouatt *et al.* (1951) found a greater percentage of active streptomycetes in the rhizosphere than in the surrounding soil. According to Khan and Williams (1975) antifungal activity was predominant among acidophilic streptomycetes common in acid soils. On the other hand, acidoduric streptomycetes inhabiting forest soils showed greater activity than neutrophiles against Gram-negative bacteria (Nkanga and Hagedorn, 1978).

Recently numerous cultures of non-streptomycetes, such as maduromycetes and actinoplanetes, have been isolated from soils and screened for new bioactive compounds (Okami and Hotta, 1988). Little attention however has been paid to the effect of soil types on the occurrence of antagonistic non-streptomycetes. The present paper describes the results of an investigation on the occurrence of antibiotic-producing microbisporae from Japanese soils characterised by different pHs.

MATERIALS and METHODS

Soil samples. A total of 117 soil samples, mainly from cultivated fields, were collected in different locations in Japan. Samples were sieved (2mm mesh) and air-dried at room temperature for 7dd. Bacterial counts were carried out by dilution plate methods (Nonomura and

Antonie van Leeuwenhoek 78: 399–405, 2000.

Rare genera of actinomycetes as potential producers of new antibiotics

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Key words: actinomycetes, antibiotics, microbial product database, strain isolation, *Streptosporangiaceae*

Abstract

A literature survey covering more than twenty-three thousand bioactive microbial products including eight thousand antiinfectives demonstrated the increasing relevance of the so called 'rare' actinomycetes as a source of new antibiotics. Past and present efforts in the isolation of rare actinomycetes have enriched the Biosearch Italia Strain Collection with more than twenty thousand strains, showing that, when selective isolation methods are developed and extensively applied, some genera, such as *Actinomadura, Actinoplanes, Micromonospora, Microtetraspora,* are not rare at all and can be recovered from many soil samples. The current focus is on the isolation of members of *Streptosporangiaceae* family, given their promising chemical diversity.

Introduction

The discovery of new molecules from actinomycetes has marked an epoch in antibiotic research and subsequent developments in antibiotic chemotherapy. Since the discovery of streptomycin, a large number of antibiotics, including major therapeutic agents such as amino glycosides, chloramphenicol, tetracyclines, macrolides and more recently β-lactam cephamycin group, have been isolated from cultures of *Streptomyces* and *Streptoverticillium* (Atlas of Actinomycetes, The Society for Actinomycetes, Japan 1997). As more new antibiotics were discovered, the chances of finding novel antimicrobial leads among conventional actinomycetes dwindled. The focus of industrial screening has therefore moved to markers of less exploited genera of rare actinomycetes such as *Actinomadura, Actinoplanes, Amycolatopsis, Dactylosporangium, Kibdelosporangium, Microbispora, Micromonospora, Planobispora Streptosporangium* and *Planomonospora.*

Several approaches have been used to drive industrial isolation programs towards the so called 'rare' actinomycetes. The development and massive application of genus-oriented selective isolation methods, mainly applied by industrial researchers, has given a significant impetus to the discovery of new microbial products of medical importance. Furthermore, this approach also helps to answer the question: are these less exploited actinomycetes less abundant in the environment or are they just more difficult to isolate and cultivate? In this paper, a survey of the microbial product literature and the role of the so called 'rare' genera of actinomycetes in the discovery of new bioactive molecules is reported. These data support and direct our efforts to improve the quality and variety of the Biosearch Italia S.p.A Microbial Collection. Some of our isolation approaches are thereby presented.

The Antibiotic Literature Database

This paper summarizes and reviews literature data obtained by querying the Biosearch Italia database, which is called the Antibiotic Literature Database (ABL). The ABL is a proprietary database designed to provide information about microbial products discovered from 1900 onwards. Data obtained from scientific journals and patent applications are entered into the ABL according to standard criteria. The database is continuously updated with information on novel compounds or additional data concerning molecules previously described. More than twenty-three thousand microbial products from bacteria and fungi are currently covered.

The ABL contains: names and synonyms, discovery institutions, natural sources, physico-chemical characteristics, biological data and molecular struc-

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Lantibiotics: structure, biosynthesis and mode of action

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Abstract

The lantibiotics are a group of ribosomally synthesised, post-translationally modified peptides containing unusual amino acids, such as dehydrated and lanthionine residues. This group of bacteriocins has attracted much attention in recent years due to the success of the well characterised lantibiotic, nisin, as a food preservative. Numerous other lantibiotics have since been identified and can be divided into two groups on the basis of their structures, designated type-A and type-B. To date, many of these lantibiotics have undergone extensive characterisation resulting in an advanced understanding of them at both the structural and mechanistic level. This review outlines some of the more recent developments in the biochemistry, genetics and mechanism of action of these peptides.

Keywords: Bacteriocin; Lantibiotic; Nisin; Lacticin 3147; Mode of action

Contents

1. Introduction

Bacteriocins are one of a number of antimicrobial substances produced by lactic acid bacteria (LAB), including organic acids, hydrogen peroxide, diacetyl and inhibitory enzymes [1,2]. The LAB have been used for centuries in the fermentation of food, not only for flavour and texture, but also due to the ability of starter-derived inhibitors to prevent the growth of spoilage and pathogenic microorganisms [3,4]. The prototype LAB bacteriocin, nisin, was first discovered in 1928, when Rogers [5] observed metabolites of *Streptococcus lactis* (now reclassified as *Lactococcus lactis*) which were inhibitory to other LAB. The commercial application of nisin in the preservation of a

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PII: S0168-6445(00)00065-6

Annu. Rev. Microbiol. 1998. 52:41–79

LANTIBIOTICS: Biosynthesis and Biological Activities of Uniquely Modified Peptides from Gram-Positive Bacteria

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KEY WORDS: antibiotic peptides, nisin, mersacidin, lantibiotic biosynthesis, peptide modifying enzymes

ABSTRACT

A plethora of novel gene-encoded antimicrobial peptides from animals, plants and bacteria has been described during the last decade. Many of the bacterial peptides possess modified building blocks such as thioethers and thiazoles or unsaturated and stereoinverted amino acids, which are unique among ribosomally made peptides. Genetic and biochemical studies of many of these peptides, mostly the so-called lantibiotics, have revealed the degree to which cells are capable of transforming peptides by posttranslational modification. The biosynthesis follows a general scheme: Precursor peptides are first modified and then proteolytically activated; the latter may occur prior to, concomitantly with or after export from the cell. The genes for the biosynthetic machinery are organized in clusters and include information for the antibiotic prepeptide, the modification enzymes and accessory functions such as dedicated proteases and ABC transporters as well as immunity factors and regulatory proteins. These fundamental aspects are discussed along with the biotechnological potential of the peptides and of the biosynthesis enzymes, which could be used for construction of novel, peptide-based biomedical effector molecules.

CONTENTS

0066-4227/98/1001-0041$08.00

ISOLATION OF THE GENUS *MICROBISPORA* FROM SOIL OF CHINA

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(*Laboratory of Electron Microscope, Sichuan Medical College, Chengdu*)

In the screening of new antibiotics, more than 300 strains of *Microbispora* were isolated from the soil samples collected from the south and southwest China and 200 strains of them were studied. An attempt was made to classify these organisms into 8 groups according to their cultural characteristics, namely, Albus, Alboviolaceus, Roseus, Roseoruber, Roseoflavus, Violaceus, Chromogenes and Flavus. Some of the isolates possess antibacterial activities.

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Sgrb

Datum/Date
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Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
Vicuron Pharmaceuticals, Inc.

COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☐ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

The following specifications given by the applicant have been approved by the Search Division:

☒ abstract ☒ title

☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.

The following figure will be published together with the abstract: 4

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 01 6306

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X Y	US 6 551 591 B1 (LEE MAY D) 22 April 2003 (2003-04-22) * the whole document *	1-21 1-21	C07K14/195 C07K2/00 C07K4/04 C12P1/06
Y	EP 0 592 835 A (SQUIBB BRISTOL MYERS CO) 20 April 1994 (1994-04-20) * the whole document *	1-21	A61K38/02 A61P31/04 A23K1/17 //(C12P1/06, C12R1:01)
Y	HAYAKAWA M ET AL: "Distribution of antibiotic-producing Microbispora strains in soils with different pHs" ACTINOMYCETES, vol. 6, no. 3, 1995, pages 75-79, XP008025139 * abstract *	1-21	
Y	XU S-Z ET AL: "Isolation of the genus Microbispora from soil of China" WEISHENGWU XUEBAO, vol. 19, no. 3, 1979, pages 255-258, XP008025262 ISSN: 0001-6209 * abstract *	1-21	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07K C12P C12R A61K A23K
Y	LAZZARINI A ET AL: "Rare genera of actinomycetes as potential producers of new antibiotics." ANTONIE VAN LEEUWENHOEK, vol. 78, no. 3-4, December 2000 (2000-12), pages 399-405, XP008025144 ISSN: 0003-6072 * abstract * * figure 3 *	1-21	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23 December 2003	van de Kamp, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 01 6306

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	DATABASE WPI Section Ch, Week 198451 Derwent Publications Ltd., London, GB; Class B04, AN 1984-316058 XP002263383 -& JP 59 198982 A (MEIJI SEIKA KAISHA), 10 November 1984 (1984-11-10) * abstract *		
D,A	MCAULIFFE O ET AL: "Lantibiotics: Structure, biosynthesis and mode of action" FEMS MICROBIOLOGY REVIEWS, vol. 25, no. 3, May 2001 (2001-05), pages 285-308, XP002209342 ISSN: 0168-6445 * the whole document *		
D,A	SAHL H-G ET AL: "Lantibiotics: biosynthesis and biological activities of uniquely modified peptides from Gram-positive bacteria" ANNUAL REVIEW OF MICROBIOLOGY, vol. 52, 1998, pages 41-79, XP001098220 ISSN: 0066-4227 * the whole document *		TECHNICAL FIELDS SEARCHED (Int.Cl.7)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23 December 2003	van de Kamp, M

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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

This application is covered by the extended European search report pilot project at present running within the European Patent Office, applied to all European patent applications filed as first filing and searched on or after 01.07.03. Under this project the EPO issues together with the search report an opinion on whether the application and the invention to which it relates meet the requirements of the EPC. This non-binding opinion is issued free of charge as a service. This opinion may be used as the basis for an informed decision as to whether it is desired to pursue the application further or not.

For further details of this pilot project, the applicant's attention is directed to the Official Journal edition 5/2003. If any further immediate questions or comments arise the EPO Customer Services: +31-70-340 4500 or +49-89-2399 2828 can be contacted.

The attached opinion reveals that the application or the invention to which it relates appear not to meet the requirements of the Convention (see comments on enclosed Form 2906).

If the applicant wishes to continue with this application the examination fee must be paid. Where appropriate amendments can be filed to address the objections raised in the opinion, thus shortening the overall procedure. If no amendments are filed, the opinion will be re-issued as the first official communication under Article 96(2) and Rule 51(2) EPC.

If the examination fee has already been paid and the right to the communication under Article 96(1) EPC has been waived for this application, the first official communication under Article 96(2) and Rule 51(2) EPC will be issued promptly.

The examination is being carried out on the **following application documents**:

Text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR LI

Description, pages:

1-40 as originally filed

Claims, No.:

1-21 as originally filed

Drawings, sheets:

1/14-14/14 as originally filed

1 Documents

The following document is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US-B1-6 551 591 (LEE MAY D) 22 April 2003
D2: EP-A-0 592 835 (SQUIBB BRISTOL MYERS CO) 20 April 1994
D3: HAYAKAWA M ET AL: 'Distribution of antibiotic-producing Microbispora strains in soils with different pHs', ACTINOMYCETES, vol. 6, no. 3, 1995, pages 75-79
D4: XU S-Z ET AL: 'Isolation of the genus Microbispora from soil of China', WEISHENGWU XUEBAO, vol. 19, no. 3, 1979, pages 255-258
D5: LAZZARINI A ET AL: 'Rare genera of actinomycetes as potential producers of new antibiotics.' ANTONIE VAN LEEUWENHOEK, vol. 78, no. 3-4, December 2000, pages 399-405

2 Article 54 EPC - Novelty

2.1 *Objection to novelty - claims 1-3*

The present application does not meet the requirements of Art. 52(1) EPC, because the subject-matter of independent **claims 1-3** is not new in the sense of Art. 54(1) and (2) EPC.

D1 discloses lanthionine- and dehydro-residue-containing antibiotics isolated from a *Microbispora sp.* strain, *Microbispora corallino*, arbitrarily denominated MF-BA-1768 (alpha1 and beta1), characterised by physical parameters (molecular weight deduced from mass spectrum, UV spectrum, IR spectrum, ^{13}C-NMR spectrum). The parameter values given for antibiotic 107891 and its components (factors A1 and A2) resemble those disclosed for MF-BA-1768 (alpha1 and beta1), and appear indiscriminately identical given the differences in recording conditions and spectral resolution. Hence, in the absence of further proof for the fact that antibiotic 107891 and/or its factors A1 and A2 is/are distinguishable from antibiotic MF-BA-1768 and/or its factors alpha1 and beta1, it is assumed that antibiotic 107891 and/or its factors A1 and A2 is/are identical with antibiotic MF-BA-1768 and/or its factors alpha1 and beta1 as disclosed in **D1**.

2.2 *Objection to novelty - claims 4-20*

The same reasoning as given under **2.1** is extended to the subject-matter of **claims 4-20**, the fact that 107891 is indiscriminately identical with MF-BA-1768 rendering the subject matter of **claims 4-20** not novel, since **D1** also discloses a process for producing the antibiotic(s) disclosed in it, the process parameters of said process as claimed in current **claims 4-15** being disclosed in **D1**, and since **D1** further discloses pharmaceutical applications of the antibiotic(s) disclosed in it, falling within the terms of current **claims 16-20**.

2.3 *Objection to novelty - claim 21*

In the absence of proof for the contrary, antibiotic 107891-producing *Microbispora sp.* ATCC PTA-5024, as claimed in **claim 21**, is assumed to be identical with or a variant or mutant of the MF-BA-1768-producing *Microbispora* strain disclosed in **D1**. The *Microbispora sp.* disclosed in **D1** is therefore considered to fall within the terms of **claim 21**.

2.4 Thus, **claims 1-21** lack novelty, contrary to Art. 54(1) EPC.

3 Article 56 EPC - Inventive Step

3.1 *Objection to inventivity*

Even if novel subject-matter could be established, the present application does not meet the requirements of Art. 52(1) EPC because the subject-matter of **claims 1-21** does not involve an inventive step in the sense of Art. 56 EPC.

(a) **D1** and **D2** are independently considered to represent the most relevant state of the art with respect to the inventivity of **claims 1-21**. **D1** and **D2** disclose antibiotics isolated from a *Microbispora sp.* strain, methods of isolation and purification, methods of use, and the producing strains.

(b) The subject-matter of **claims 1-21** differs primarily from **D1** in that a purportedly novel antibiotic and producing strain is claimed, and from **D2** that a distinctly novel antibiotic and producing strain is claimed.

(c) The problem to be solved by the present application may therefore primarily be regarded as providing a further antibiotic, as well as a further producing strain.

(d) The solution as proposed is the antibiotic 107891 as claimed in **claims 1-3**, as well as methods of isolation and purification from a *Microbispora sp.* strain, methods of use, and the producing strain, according to **claims 4-21**.

(e) This solution cannot however be considered as involving an inventive step for the following reason:

- **D3-5** independently disclose that *Microbispora spp.* strains are well-known producers of antibiotics. The person skilled in the art will therefore seriously consider, in order to solve the problem, to further screen *Microbispora spp.* strains in order to isolate a further antibiotic from them, using appropriate isolation,

purification, and characterisation methods falling within the knowledge and ability of the skilled person. In the absence of any special technical effect, the antibiotic 107891 as well as methods for its isolation, purification, characterisation, and use, as well as its producing strain, therefore represent a mere selection from a known reservoir which the skilled person will explore in order to solve the problem posed, thereby rendering the solution non-inventive.

Thus, **claims 1-21** lack inventivity, contrary to Art. 56 EPC

4 Concluding matters

4.1 *Request for new claims*

It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 29(1) EPC. Any amendments should comply with Art. 123(2) EPC. The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art, particularly **D1**, and the significance thereof.

4.2 *Identification of amendments*

In order to facilitate the examination of the conformity of the amended application with the requirements of Art. 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.
If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

4.3 *New information*

Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be

confined to the letter of reply and not be incorporated into the application (Art. 123(2) EPC and Guidelines, C-VI, 5.7 et seq.).

Mart van de Kamp

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO. EP 03 01 6306

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

23-12-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6551591 B1	22-04-2003	NONE	
EP 0592835 A	20-04-1994	AU 4746593 A	31-03-1994
		CA 2106446 A1	24-03-1994
		EP 0592835 A2	20-04-1994
		JP 6211615 A	02-08-1994
JP 59198982 A	10-11-1984	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
G69277/RS/sgh		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2004/007658	12/07/2004	18/07/2003
Applicant		
VICURON PHARMACEUTICALS INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1B
      [X] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

Intern[illegible]al application No.
PCT/E[illegible]/007658

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] in written format

   [X] in computer readable form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [X] filed together with the international application in computer readable form

   [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007658

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/195 C07K2/00 C07K4/04 C12P1/06 A61K38/02
A61P31/04 A23K1/17
//(C12P1/06,C12R1:01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12P C12R A61K A23K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 551 591 B1 (LEE MAY D) 22 April 2003 (2003-04-22) the whole document	1-23
A	EP 0 592 835 A (SQUIBB BRISTOL MYERS CO) 20 April 1994 (1994-04-20) the whole document	1-23
A	HAYAKAWA M ET AL: "Distribution of antibiotic-producing Microbispora strains in soils with different pHs" ACTINOMYCETES, vol. 6, no. 3, 1995, pages 75-79, XP008025139 abstract	1-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2004	16/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van de Kamp, M

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	XU S-Z ET AL: "Isolation of the genus Microbispora from soil of China" WEISHENGWU XUEBAO, vol. 19, no. 3, 1979, pages 255-258, XP008025262 ISSN: 0001-6209 abstract	1-23
A	LAZZARINI A ET AL: "Rare genera of actinomycetes as potential producers of new antibiotics." ANTONIE VAN LEEUWENHOEK, vol. 78, no. 3-4, December 2000 (2000-12), pages 399-405, XP008025144 ISSN: 0003-6072 abstract figure 3	1-23
A	DATABASE WPI Section Ch, Week 198451 Derwent Publications Ltd., London, GB; Class B04, AN 1984-316058 XP002263383 -& JP 59 198982 A (MEIJI SEIKA KAISHA) 10 November 1984 (1984-11-10) abstract	
A	MCAULIFFE O ET AL: "Lantibiotics: Structure, biosynthesis and mode of action" FEMS MICROBIOLOGY REVIEWS, vol. 25, no. 3, May 2001 (2001-05), pages 285-308, XP002209342 ISSN: 0168-6445 cited in the application the whole document	
A	SAHL H-G ET AL: "Lantibiotics: biosynthesis and biological activities of uniquely modified peptides from Gram-positive bacteria" ANNUAL REVIEW OF MICROBIOLOGY, vol. 52, 1998, pages 41-79, XP001098220 ISSN: 0066-4227 cited in the application the whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2004/007658

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 6551591 B1	22-04-2003	NONE		
EP 0592835 A	20-04-1994	AU	4746593 A	31-03-1994
		CA	2106446 A1	24-03-1994
		EP	0592835 A2	20-04-1994
		JP	6211615 A	02-08-1994
JP 59198982 A	10-11-1984	NONE		